Chapter

Chronic Spontaneous Urticaria – Diagnosis and Management

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Abstract

Chronic urticaria can be subclassified into chronic spontaneous urticaria and chronic inducible urticaria. Up to 30% of cases are associated with functional immunoglobulin G antibodies to the high affinity immunoglobulin E receptor FcεRIα or to immunoglobulin A. Pathogenic activation of mast cells and basophils gives rise to release of pro-inflammatory mediators that lead to development of hives. CSU is a debilitating disease with a relapsing course. It affects 0.5–1% of the population at any given time. The duration of CSU is generally 1–5 years but can be longer in cases associated with angioedema and autoreactivity. CSU has detrimental effects on life quality with sleep-deprivation and psychiatric disorders being the most frequent. In a great number of patients an underlying cause or eliciting factor cannot be identified. Among the patients in which an aetiology is suspected, infections, medication, food and psychological factors are most commonly associated. A potential autoimmune cause has been reported in up to 50% of patients. Chronic inducible urticaria is characterised by its ability to be triggered consistently and reproducibly in response to a specific stimulus (pressure, temperature, vibration, water, heat, light). Antihistamines form the mainstay of therapy. In recalcitrant chronic urticaria, a variety of other drugs have been tried.

Keywords: Wheals, Angioedema, Chronic Spontaneous Urticaria, Chronic Inducible Urticaria, Classification, Prevalence, Histamine-mediated, Pathophysiology, anti-IgE, anti-FcεRI, Autoallergy, anti-TPO, Autoimmune urticaria, Vitamin D, Pseudoallergens, Stress, associated conditions, Predictors of severity, Diagnosis, Medical History, Histopathology, Check List, Clinical signs, Differential Diagnosis, Guidelines, Patient reported outcomes, UAS7, DLQI, Socio-economic burden, Patient characteristics, real-world study, Refractory chronic urticaria, Treatment, Antihistamines, Omalizumab, Leukotriene receptor antagonist, oral corticosteroids

1. Introduction

Chronic urticaria can be subclassified into chronic spontaneous urticaria and chronic inducible urticaria. Up to 30% of cases are associated with functional immunoglobulin G antibodies to the high affinity immunoglobulin E receptor FcεRIα or to immunoglobulin A. Pathogenic activation of mast cells and basophils gives rise to release of pro-inflammatory mediators that lead to development of hives. CSU is a debilitating disease with a relapsing course. It affects 0.5–1% of the

population at any given time. The duration of CSU is generally 1–5 years but can be longer in cases associated with angioedema and autoreactivity. CSU has detrimental effects on life quality with sleep-deprivation and psychiatric disorders being the most frequent. In a great number of patients an underlying cause or eliciting factor cannot be identified. Among the patients in which an aetiology is suspected, infections, medication, food and psychological factors are most commonly associated. A potential autoimmune cause has been reported in up to 50% of patients. Chronic inducible urticaria is characterised by its ability to be triggered consistently and reproducibly in response to a specific stimulus (pressure, temperature, vibration, water, heat, light). Antihistamines form the mainstay of therapy. In recalcitrant chronic urticaria a variety of other drugs have been tried that include leukotriene receptor inhibitors, conventional immunosuppressive systemic therapy, anti-inflammatory and biologic therapy. In this chapter we give an overview of CU and CSU in particular and discuss its diagnosis and management.

2. Definition

Urticaria is a relatively common condition that can persist for weeks, months or years and can affect significantly quality of life [1]. It is a heterogenous skin disorder that can be acute or chronic, intermittent or persistent and can occur alone or in association with other related conditions. The aetiology is often difficult to determine particularly in chronic urticaria[1].

Urticaria is characterised by the development of wheals, angioedema or both on the skin [2]. It is characterised by 3 features [3]:

1. Localised erythema and swelling of upper dermal layers

2. Itching and burning sensation of the skin

3. Transient nature – wheal resolves without scarring and skin returns to normal within 1–24 hours

Angioedema [3] is characterised by sudden onset localised swelling of submucosal surfaces of the upper respiratory and gastrointestinal tract, deeper dermal layers of skin including subcutaneous tissue [4]. It is associated more with pain and burning rather than itching and generally takes longer – up to 72 hours - to resolve [3].

Wheals can occur in combination with angioedema in 40% and angioedema can be the only manifestation of urticaria in 20% of patients [1, 5].

Urticaria are classified into 2 major categories [2, 3, 5] – acute vs. chronic – according to duration, and - spontaneous vs. inducible - according to aetiology [5]. Acute urticaria resolves in less than 6 weeks. Chronic urticaria lasts for longer than 6 weeks (**Table 1**).

Many cases of acute urticaria (AU) resolve but 20–45% continue and become chronic [5]. The most common causes for acute urticaria include acute viral infections and allergic reactions to food, medication, latex and insect bites [5, 6].

Chronic urticaria (CU) are clinically subdivided into spontaneous (CSU) - no specific eliciting factor(s) can be identified [7] - and inducible (CINDU) when specific identifiable stimuli trigger urticaria [7].

In summary CSU is characterised by spontaneous occurrence of wheals and or angioedema for 6 or more weeks, resulting from unidentified causes and pathophysiology that is not completely understood [3]. While autoimmune disease (21%), chronic infection (29%), and immune dysfunction (4%) may become evident over

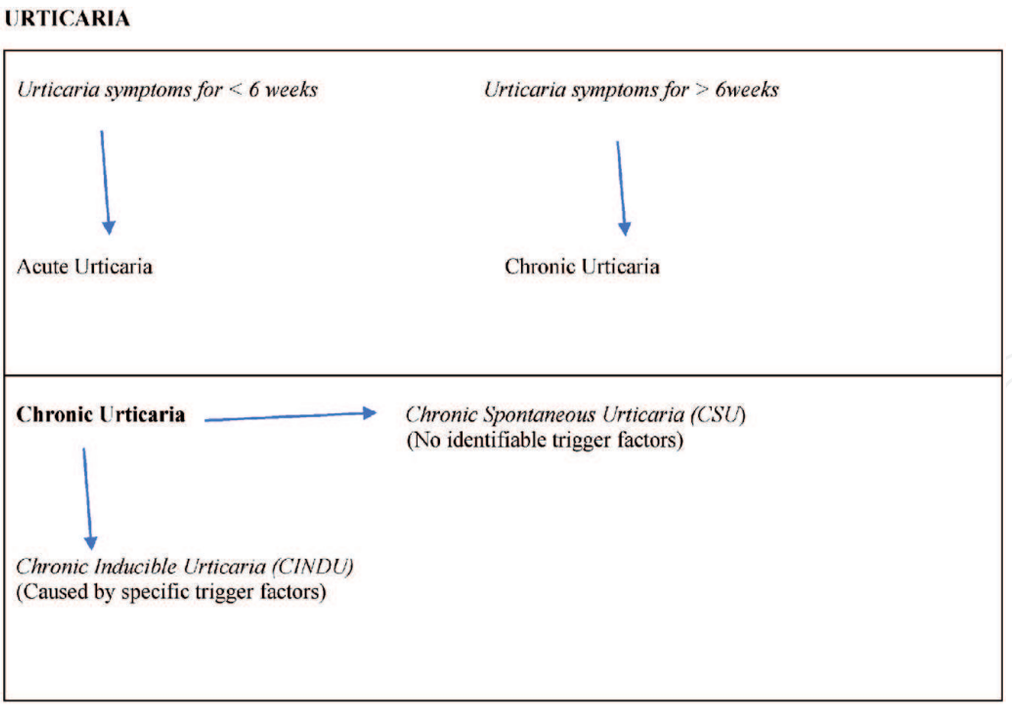

Table 1.
Classification of urticaria [2].

time, in 45% of CSU cases no underlying cause can be found even after 10-year follow-up [4, 5, 8]. In these cases, anaphylaxis does not occur even if angioedema may be present [1, 4].

It is worth mentioning that the term CSU replaced the terms chronic idiopathic urticaria and chronic autoimmune urticaria, whereas the term CINDU replaced the terms physical urticaria and other forms of inducible urticaria, such as cholinergic and aquagenic urticaria [6].

Two or more different subtypes of urticaria may coexist in any given patient. There is often overlap between CSU and CINDU [3, 5].

3. Epidemiology, underlying pathogenesis and trigger factors

3.1 Epidemiology

Evidence suggests [9] that the prevalence of CSU is geographically heterogenous, high in all groups and increasing. It is just as common in children as it is in adults [9]. Lifetime prevalence is 9% [5] with an overall point prevalence in all age groups estimated at 0.7% [4, 9]. The point prevalence is higher in women than in men (1.3% vs. 0.8%) [4, 9] but same in children (1.1% boys vs. 1% girls) [9]. CSU is more common in adolescents and the commonest subgroup of CU [2]. It has a lifetime risk of 20% [7] and is self-limiting with an average duration of 2–5 years, although in up to 30% of patients the symptoms may persist for >5 years [10].

3.2 Underlying pathogenesis

There is little doubt that the release of histamine by mast cells (MC) and basophils represent the final stage in the pathogenesis of CU cases [4]. There is however still uncertainty about the factors that activate these cells and lead to cell degranulation

[11]. Several lines of evidence suggest that different biologic systems like immunity, inflammation and coagulation may contribute to wheal development [4, 11].

There are immunologic and non-immunologic mechanisms that lead to MC degranulation and release of mediators including histamine, leukotrienes and prostaglandins [4, 6]. These mediators recruit basophils, eosinophils, polymononuclear cells and lymphocytes [4, 6] and cause the typical skin manifestations of (a) pruritus via sensory nerve stimulation, (b) vascular dilatation and permeability that leads to extravasation and (c) oedema in upper dermis (wheals) and lower dermis/subcutaneous tissue (angioedema) [6].

The **non-immunologic** pathogenesis involves dysregulation of intracellular signalling pathways within MCs and basophils that lead to defects in trafficking and function of these cells [4]. The immunologic pathway involves the development of autoantibodies to IgE or the high affinity IgE receptor FcεRIα on MCs and basophils [4, 9].

Two types of **immunological CSU** have been identified namely Type I and Type IIb [9]:

- Type I autoimmune CSU is driven by anti-IgE antibodies to autoallergens while
- Type IIb autoimmune CSU is due to autoantibodies that target directly and activate MC degranulation

In type I autoimmune CSU, autoantigens crosslink IgE autoantibodies and bind on MCs and basophils to cause release of vasoactive mediators. Thyroperoxidase (TPO) is the commonest autoallergen binding to IgE (IgE-anti-TPO), other autoantigens include thyroglobulin, tissue factor and IL-24 [4, 9]. Furthermore, some studies have demonstrated that the raised IgE autoantibodies contribute to the increased total serum IgE level found in CSU patients [4, 9].

In type IIb autoimmune CSU, autoantibodies of IgG or IgM type bind to antigen on the target cell (MC) and cause release of mediators. Furthermore, IgG and to a lesser degree IgM and IgA autoantibodies to IgE high affinity receptor FcεRI on MCs and basophils have been identified in roughly 50% of CSU [5, 9]. CSU patients show positive reaction to autologous serum skin test (ASST), that is flare and wheal development to intradermal injection of patient's own serum [4, 9, 12].

Some evidence suggests that type I and IIb autoimmune CSU differ in their clinical features, laboratory markers and response to therapy [9, 13]. Type IIb autoimmune CSU is thought to exhibit higher disease activity, longer duration, higher rates of associated autoimmunity and eosinopenia and basopenia, both markers of recalcitrant disease [9, 13].

CSU is characterised by a **systemic pro-inflammatory state** [11]. Many patients have slightly raised levels of C-reactive protein [8, 13]. Studies [4, 11] also suggest higher association with metabolic syndrome, hyperlipidemia, Multiple sclerosis and other autoimmune conditions (Rheumatoid arthritis, Systemic Lupus Erythematosus) [4, 9].

3.3 Trigger factors

Higher emotional stress is known to contribute to low grade inflammation [8]. Patients with CSU are reported to experience higher rates of anxiety, depression and somatiform disorders [5], although it is unclear if they are cause or effect of CSU [8]. Psychiatric comorbidity has been linked as an additional factor that affects quality of life in CSU patients [5, 12].

Coagulation pathway: Specific studies have demonstrated that the coagulation pathway is activated in CU and involves first the extrinsic pathway followed by

the intrinsic pathway. This activation of coagulation pathway is thought to be an intermediate step in CSU pathophysiology [4, 11].

Drugs have been implicated in CU development. The commonest include angiotensin- converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 5]. NSAIDs are an aggravating factor in 12–30% of CSU patients [3, 5]. They can also induce urticaria/angioedema in the absence of urticaria history [5]. ACE inhibitor – induced urticaria/angioedema is caused by non-immunologic accumulation of bradykinin and other neurokinins [5] and can occur from weeks to years after ACE inhibitor therapy is commenced.

Food: Type I food allergy is a rare cause of CSU. It should be considered in patients with intermittent symptoms and within 1 hour of exposure to food [5]. The role of food additives as a cause of CSU is unclear. Some studies demonstrated resolution of CSU symptoms after 14 days of pseudoallergen avoidance in up to 30% of patients [5, 8, 14]. Low serum Vitamin D levels and vitamin D supplementation has been reported to improve small numbers of recalcitrant CSU [8, 15].

Infections have been implicated as cause of CSU and include bacterial, viral, parasitic and fungal organisms. Frequency and relevance depend on local population and geographic location [5]. *Anisakis simplex*, a sea fish nematode is relevant in the Mediterranean in the context of CSU [5, 16]. *Helicobacter Pylori* (HP) gastritis has been reported in association with CSU and some studies have reported CSU improvement with HP eradication [3, 5, 8, 17] (**Table 2**).

3.3.1 Contact urticaria

Not all urticaria are mast cell or histamine dependent. Contact urticaria to sorbic acid, methyl nicotinate, cinnamic acid, cinnamic aldehyde and dimethyl sulfoxide are thought to be due to prostaglandins released directly from the epidermis. They do not respond to treatment with antihistamines but improve with salicylic acid and NSAIDs [5].

3.3.2 CINDU

In *CINDU* signs and symptoms usually are elicited by a specific factor and occur in exposed areas that are reproducible by provocation tests [5, 9]. Diagnosis is based on patient history and provocation tests [5] where possible.

Associated Factors that affect prevalence and severity of CSU	
Factor (s)	*Effect (s)*
Autoimmunity	Predisposes to CSU
Food additives/pseudoallergens	Facilitates CSU
Increased stress	Predisposes & Facilitates CSU
Parasitic infection	Predisposes to CSU
Helicobacter Pylori gastritis	Predisposes to CSU
Metabolic Syndrome	Pro-inflammatory state
Low Vitamin D3	Facilitates CSU
Dysbiosis of GI-Tract	Predisposes to CSU

Table 2.
CSU associated factors [8].

Chronic INDuced Urticaria (CINDU) occur when identifiable stimuli trigger urticaria
• Symptomatic Dermographism (mechanical shearing forces, hives arise after 1-5 min)
• Cold Urticaria (cold air, cold water, cold wind)
• Delayed Pressure Urticaria (vertical pressure, hives arise within 3–8 hours)
• Contact Urticaria (urticariogenic substances)
• Aquagenic Urticaria (water)
• Solar Urticaria (UV and/or visible light)
• Heat Urticaria (localised heat)
• Vibratory Urticaria/Angioedema (vibratory forces e.g. pneumatic hammer)
• Cholinergic Urticaria (by increase of body temperature)
Diagnosis of CINDU is based on clinical history and where possible as result of provocation tests. It is paramount to identify accurately the specific trigger factor, confirm the diagnosis and assess the disease activity.
• Two or more different subtypes of urticaria can coexist in any given patient.
• Often there is overlap between CINDU and CSU.

Table 3.
List of different types of CINDU and their associated eliciting factors [5, 7, 10].

Patients can develop systemic signs during provocation testing including nausea, vomiting, diarrhoea, vertigo, wheezing and even anaphylactic shock [5]. CINDU is responsible for 20–30% of all CU and can be associated with CSU in 14–36% (**Table 3**) [2, 4, 5, 9].

4. Diagnosis of urticaria - medical history, clinical signs and symptoms, histopathology, laboratory testing and associated conditions

4.1 Medical history

Urticaria is characterised by the presence of wheals or angioedema. A detailed history and physical examination are essential for correct urticaria diagnosis and appropriate therapy. They help to exclude alternative diagnoses and are guide to what additional investigations are required.

An easy tool checklist for establishing a complete medical history for CU can be seen in **Table 4**.

4.2 Clinical signs and symptoms

CSU is characterised by the onset of pruritic hives and/or angioedema. Hives are well circumscribed areas of non-pitting oedema with blanched centres and raised borders that involve only superficial portion of the dermis and occur with surrounding skin erythema [4]. Wheals can be anywhere on the body and can be distributed widely [2, 5] (**Figure 1**). They can be a few millimetres to several centimetres in diameter, red or white in colour although they are bright red when they flare [4] (**Figures 2** and **3**). They can last from few minutes to several hours, can take any shape or form and can change shape before they resolve. They can be round and form rings or giant patches. They can have a map-like pattern [2]. The wheals tend to resolve in less than 24 hours and can occur at certain times during the day [2]. Hives are more persistent in CSU than CINDU.

Checklist for complete CU Medical History
1. *Time of disease onset: > < 2 hours*
2. *Duration of wheals: > < 24 hours*
3. *Shape, size, colour and distribution of wheals*
4. *Associated Angioedema*
5. *Associated subjective symptoms (itching, pain, burning)*
6. *Diurnal and nocturnal variation*
7. *Occurrence during weekends, holidays or foreign travel*
8. *Family and past medical history of urticaria or atopy*
9. *Past medical history of internal diseases, infections, known allergies*
10. *Psychosomatic and psychiatric disorders*
11. *Gastric or intestinal problems*
12. *Surgical implantation or events during surgery or after local anaesthesia*
13. *Induction by physical stimuli or exercise*
14. *Use of medication (NSAIDs, ACE-inhibitors, immunisations, hormones, laxatives, eye and ear drops, alternative remedies)*
15. *Observed correlation with food intake*
16. *Relationship to menstrual cycle*
17. *Smoking habits (perfumed tobacco products or cannabis)*
18. *Type of work (health care, agriculture, dairy and veterinary work, hairdressers, food handlers, plumbers, packers, painters through exposure to cyclic anhydrites)*
19. *Hobbies*
20. *Stress*
21. *Impact on quality of life by urticaria/angioedema (UAS7, AAS)*
22. *Prior treatment and response to treatment*

Table 4.
Checklist for establishing a complete medical history for CU [2, 3, 5].

Figure 1.
Widely distributed wheals (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Figure 2.
Solitary wheal (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Figure 3.
Solitary wheal in higher power (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Dermographism (**Figures 4** and **5**) is inducible and comprises of wheal development when the skin is stroked. It can occur on its own but also in the context of CSU and CINDU. When elicited it can support the diagnosis of urticaria.

Angioedema is more often localised and commonly affects the face in perioral and periorbital distribution, the lips, tongue, eyelids, hands, feet, genitalia and rarely bowel [2, 5]. Lesions tend to be fainter in colour and often painful (**Figure 6**). It can occur in combination with wheals.

Up to 16% of CU patients can experience systemic symptoms during a flare [5]. Systemic symptoms include fatigue, arthralgia and abdominal pain (30%), but also headache, myalgia, retrosternal oppression, wheezing, dyspnoea, rhinorrhoea, flushing, palpitations, and ocular irritation [2, 5, 16].

Figure 4.
Dermographism (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Figure 5.
Dermographism - higher power (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Physical examination should include assessment of skin [2, 5, 8, 9] for:

- the presence of wheals and angioedema
- provocation of dermographism
- any signs of purpura
- evaluation of residual lesions in areas hard to reach for patient (urticarial vasculitis)
- any signs of any underlying and/or associated conditions.

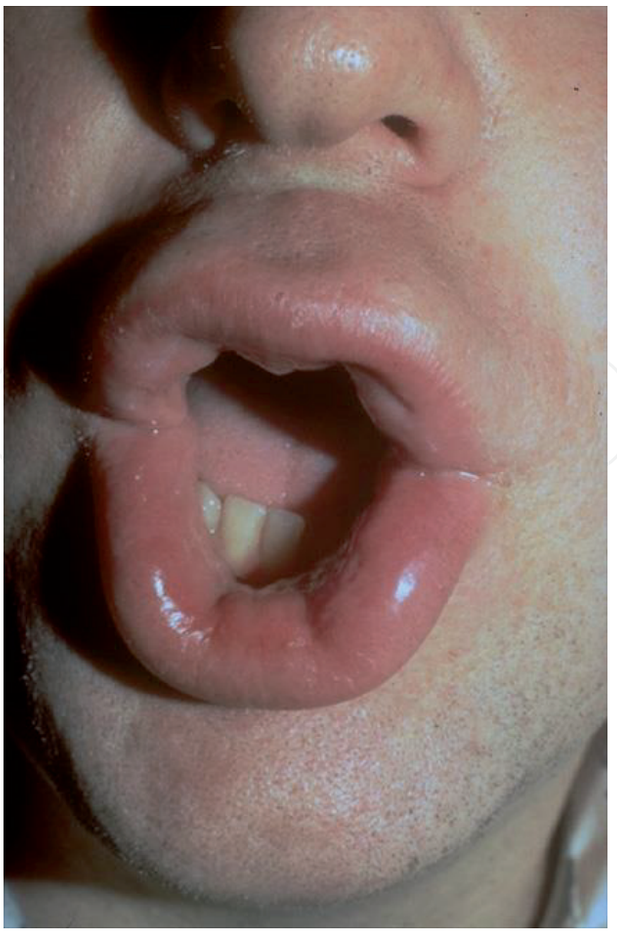

Figure 6.
Angioedema of lips (courtesy of Dr. Stephen Orpin, Solihull hospital, Birmingham).

Conditions that are associated with urticaria +/– angioedema
Syndromes presenting with urticaria +/– angioedema:
• Cryopyrin – associated periodic syndromes including familial autoinflammatory syndrome • Muckle - Wells syndrome • Neonatal – onset multisystem inflammatory disease • Chronic infantile neurologic, cutaneous and articular syndrome • Schnitzler syndrome • Gleich syndrome • Phospholipase Cg2 – associated antibody deficiency
Diseases related to urticaria:
• Urticarial Vasculitis • Serum-sickness like reaction • Bradykinin-mediated angioedema including hereditary angioedema and ACE-inhibitor induced angioedema • Urticaria Pigmentosa (Maculopapular Cutaneous Mastocytosis) • Bullous Pemphigoid (during pre-bullous stage) • Exercise induced anaphylaxis • Antropod bites
Hives are not always itchy and are often flatter in appearance

Table 5.
Diseases that can present with urticarial lesions [2, 5].

4.3 Histopathology

Histopathologic findings are usually mild and include sparse perivascular and interstitial mixed inflammatory infiltrate and upper dermal oedema [5]. If vascular damage is present urticarial vasculitis (UV) needs to be excluded. UV affects the superficial vascular dermal plexus and shows subtle features of leucocytoclastic vasculitis [5].

4.4 Laboratory testing and associated conditions

The diagnosis of CU is often made on clinical grounds, a limited routine diagnostic work-up is recommended in a case-by-case basis [5, 8]. A skin biopsy should be considered in patients that do not respond to H1 antihistamines, and when an alternative diagnosis is considered (**Table 5**) [5].

5. Disease activity scores used in chronic urticaria and burden of disease

5.1 Disease activity scores used in chronic urticaria

CSU affects several domains of health-related quality of life, such as daily living, sleep, emotional and psychological well-being as well as work productivity [9, 18]. Several types of patient-reported-outcome (PRO) instruments have been used to assess quality of life and disease burden in CSU. They include:

- ED-5D (generic)
- Dermatology Life Quality Index (DLQI) (generic dermatological)
- Disease-specific Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)
- Angioedema Quality of Life Questionnaire (AE-QoL)
- Urticaria Activity Score (UAS) (**Table 6**)
- Angioedema Activity Score (AAS)
- Urticaria Control Test (UCT)

The inclusion of PRO instruments in clinical practice is increasingly recommended by clinicians and commissioners as it allows patient input and view of their disease

The Weekly Urticaria Activity Score (UAS7)	
Wheals Score	*Pruritus Score*
0 = No wheals	0 = None
1 = Mild (< 20 wheals)	1 = Mild (present but not annoying or troublesome)
2 = Moderate (20–50 wheals)	2 = Moderate (troublesome but does not interfere with normal daily activity or sleep)
3 = Intense (>50 wheals)	3 = Intense (severe itch, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Table 6.
UAS7 = score for hives + score for itch = daily score; repeat daily assessments for 7 days and add up daily scores for UAS7 [2, 18].

and response to therapy and can contribute to better informed treatment decisions and improve physician-patient communication.

The UAS (**Table 6**) is a diary-based PRO measure that assesses the key sign hives and the key symptom itch of CU. The international EAACI/GA^{2}LEN/EDF/WAO guidelines for urticaria recommend the use of UAS in clinical practice to determine disease activity and response to treatment [9, 13, 18]. The UAS is calculated as the sum of the daily number of wheals and the pruritus severity score over a period of 7 days (UAS7). Currently two versions exist of the daily UAS7 – in the first version patients score themselves once per day (every 24 hours), in the second version the scoring happens twice daily (every 12 hours). No significant difference [18] has been identified between the two versions. It is recommended that the same version be used consistently in the same patient in order to be able to evaluate the results [16]. In current clinical practice most use the once daily scoring version, as it is less burdensome for patients. The Urticaria Control Test (UCT) is a retrospective tool consisting of four questions with a clear cut-off scoring for "well-controlled" vs. "poorly controlled" [6].

In regular clinical practice the PRO instruments commonly used to assess CU disease activity, disease control and effects on quality of life include the UAS7 and the DLQI [2].

5.2 Burden of disease

CU has significant negative impact on quality of life due to its debilitating symptoms [19, 20]. In addition to classic symptoms, like pruritus and wheals, other factors can be equally relevant to the patient, such as the unpredictability of flares, sleep disorders, fatigue, drug related side effects and physical appearance [21]. A major impairment is observed in patients with the highest disease activity and in patients with autoimmune urticaria [21]. Undertreated patients report high disease burden that leads to higher economic burden due to absence or presenteeism - reduced capacity while - at work and higher utilisation of health care resources [19, 20]. Itching and angioedema are the main reasons affecting capacity at work causing presenteeism [22].

Other reasons that contribute to high socio-economic burden include an often considerable delay in diagnosis and specialist referral [22], the inadequate knowledge about CSU in primary and secondary care, and high cost for unnecessary investigations and treatments due to poor adherence to guidelines and best practice [22].

6. Treatment of chronic urticaria

The aim of CU therapy is symptom control as no cure is available to date. Often management of CSU and CINDU overlap. Approach to CU management [2, 10, 19] consists of:

1. Identification and elimination or treatment of underlying causes and associated conditions

2. Avoidance of any known aggravating trigger factors including NSAIDs, ACE-Inhibitors, physical stimuli where possible

3. Pharmacological therapy to prevent MCs degranulation of mediators and their effects [2]

Investigations to rule out any underlying inflammatory or infectious diseases should be initiated on a case-by-case basis. Plasmapheresis has been shown to provide temporary improvement in some autoantibody positive patients with refractory CSU [2] by reducing functional autoantibodies.

Two major professional bodies have published guidelines [1, 19] for the evaluation and management of urticaria. The US JTF Practice Parameter recommends a 4-step approach to management (**Table 7**), whereas the EAACI guidelines (**Table 8**) advocate a 3-step approach. Both guidelines concur in that first line therapy for acute and chronic urticaria should focus on the use of non-sedating 2nd generation H1 antihistamines (SGAs).

The European guidelines differ from the US guidelines in that treatment with sedating 1st generation H1 antihistamines (FGAs) and H2 antihistamines are not recommended. In addition, European guidelines regulate Leukotriene Modifying Agents (LTMAs) to the last Step 3 treatment, whereas US guidelines recommend these agents to be used earlier as adjunctive Step 2 [1].

Although both the US and the European urticaria guidelines recommend a step-by-step approach to CU therapy, patient specific parameters such as serologic, clinical or histological findings are not considered. To date no clinically effective treatment algorithm exists for CU that is based on patient specific parameters [19].

Finally, both the US and European urticaria treatment guidelines should be used with caution and might require adaptation in children, pregnant/lactating women, and elderly patients with CU, as drug doses may have to be reduced or might be contraindicated [1, 2, 19].

US urticaria guidelines to therapy approach
• Begin therapy at the step that is appropriate for individual patient considering urticaria severity and previous treatment history
• Medication should be assessed at each step for efficacy and adverse effects
• Once adequate control has been achieved it is appropriate to step down treatment
Step 1
• Start Monotherapy with non-sedating 2nd generation antihistamine (SGA)
• Avoid any trigger factors (NSAIDs, ACE-Inhibitors) and relevant physical stimuli
Step 2 One or more of the following can be used simultaneously:
• Increase up to fourfold the dose of SGA used in Step 1
• Add another SGA
• Add a H2-antagonist
• Add leukotriene receptor antagonist
• Add 1st generation antihistamine (FGA) to be taken at bedtime
Step 3 Advance dose of FGA (hydroxyzine or doxepin) as tolerated
Step 4 Alternative treatment can be added:
• Omalizumab or cyclosporine
• Other anti-inflammatory agents, immunosuppressants, biologic therapy

Table 7.
Adapted from JTF practice parameters "The diagnosis and management of acute and chronic urticaria: 2014 update" [1].

EAACI Urticaria guidelines to treatment approach

First Line

Monotherapy with 2nd generation antihistamines

If no improvement after 2 weeks

Second Line

Increase dose up to fourfold of 2nd generation antihistamine used as first line

If symptoms persist after another 1- 3 weeks

Third Line

Add one of the following second line agents:

- Omalizumab
- Cyclosporine
- Montelukast

Short course of oral corticosteroids (up to 10 days) can be used at all times during a severe flare

Table 8.
Adapted from EAACI urticaria guideline for the definition, classification, diagnosis and management of urticaria: 2013 revision [1].

6.1 H1-antihistamines

There is good evidence for the use of second-generation antihistamines (SGAs) as first line therapy in mild to moderate CU [1, 7, 19]. SGAs like cetirizine, levocetirizine, loratadine, desloratadine fexofenadine, azelastine, bilastine have a good safety, efficacy and tolerability profile. Over 50% of CU do not respond to the licenced dose of SGAs. For these patients 2–4 times higher than licenced dose is well tolerated and considered acceptable [1, 2, 10, 19]. First generation antihistamines (FGAs) are effective but due to their sedating effect and possible interference with daily activities they are not preferred choice. Side effects include excessive dryness, constipation (due to anticholinergic activity) and occasional Torsades de Pointe (especially linked to astemizole and terfenadine). About 30% of patients continue to experience CU symptoms despite maximal tolerated doses of SGAs [1, 2, 10, 19, 23] and are classified as non-responders [23].

6.2 H2-antihistamines

H2- Antihistamines can be added to H1-antihistamine monotherapy if they prove ineffective. Cimetidine has been shown to increase the half-life of H1-antihistamines [19]. Ranitidine was shown in a Cochrane review to be more

effective in combination with diphenhydramine than diphenhydramine on its own [19]. The opinion about their use in combination with H1-antihistamines in the treatment of CU is however divided and is reflected in the difference of recommendation between the US and European urticaria guidelines (**Table 7** vs. **Table 8**). Doxepin a tricyclic antidepressant has combined H1 and H2 and muscarinic blocking activities. It has been shown to be effective in as high as 43% of patients who are recalcitrant to high dose antihistamines therapy [10, 23]. It can be given in doses of 25–50 mg at night or 10-25 mg 3–4 times per day.

6.3 Leukotriene modifier agents (LMAs)

LMAs are leukotriene receptor antagonists and include montelukast and zafirlukast as well as the 5-lipoxygenase-inhibitor zileuton. Several RCTs on CU therapy showed mixed results and thus firm recommendations are not available. However, due the good safety profile of LMAs they might be considered an alternative addition in CU patients who are refractory to antihistamines therapy [17, 24] (**Table 7**). Predictors of good response to LMAs include urticaria triggered by Aspirin, NSAIDs, food additives or pseudoallergens and autoimmune urticaria with positive autologous serum skin prick test [1, 10, 19, 25]. Montelukast can be used in doses of 10 mg/day [10].

6.4 Oral corticosteroids (OCTs)

Large control studies are not available on the use of OCTs in CU. However, OCTs show high efficacy in recalcitrant CU and are used for short term and at the lowest effective dose for severe flares. Long term use of OCTs in CU is not recommended due the multitude of known significant adverse effects [1, 2, 10, 23]. Tapering of OCTs dose is not needed if the patients take <40 mg daily dose and for a period of up to 3 weeks [19]. Oral mini pulses with methyl prednisolone 16 mg tablets twice weekly for 2 months and in combination with H1-antihistamines showed significant reduction in mean UAS7 in a small number of patients [10].

6.5 Immunosuppressive agents (IAs)

IAs should be considered in the case of OCTs therapy being required for longer periods of time. Ciclosporin is the most studied medication and is recommended to be used either at a weight-based dose of 4 mg/kg/per day or at a daily dose of 200 mg for a period of 16 weeks [1, 2, 10, 19]. Improvement in UAS can be as early as 2 weeks of commencing treatment and complete remission occurs in 3 out of 4 patients [10] particularly in autoimmune associated CSU. Regular monitoring is required due to the risk of significant adverse effects and it is reserved in the treatment of severe refractory CSU. Other IAs include:

- Methotrexate
- Mycophenolate Mofetil
- Azathioprine
- Mizoribine
- Intravenous or oral Cyclophosphamide

6.6 Alternative agents

Alternative Agents have also been anecdotally used in refractory CSU and may be of value to individual patients and in certain clinical circumstances [1, 2, 5, 24]. These agents include:

- Dapsone
- Sulfasalazine
- Hydroxychloroquine
- Colchicine
- Intravenous Immunoglobulins
- Plasmapheresis

6.7 NB-UVB therapy

NB-UVB Therapy has been shown in combination with levocetirizine to significantly reduce urticaria activity and to have a long-lasting positive effect on UAS7 [10, 19]. PUVA and BB-UVB have so far shown mixed to neutral results [19].

6.8 Biologic agents

Omalizumab is licenced for the treatment of CU in adults and adolescents that continue to be symptomatic despite the use H1 antihistamines therapy.

Omalizumab is a recombinant humanised IgG monoclonal antibody against the Fc portion of the IgE antibody. It prevents free IgE binding to the high affinity IgE receptor FcεRI and downregulates these receptors on MC and basophils [4, 19]. It has been shown to be effective and well tolerated in 3 phase III and 2 phase II studies at doses from 150 to 300 mg every 4 weeks independent of total serum IgE level or body weight [2, 19]. Omalizumab improves angioedema and quality of life, is suitable for long-term use, and treats relapse after discontinuation [2]. 35–40% of patients achieve complete relief and another 30% reported partial relief after 3 and 6 months [2, 4]. The recommended dose is 300 mg by subcutaneous injection every 4 weeks. Some patients may achieve symptom control with a dose of 150 mg subcutaneous injection every 4 weeks [2]. If no therapeutic response is seen within 6 months of treatment efficacy is unlikely to be achieved and omalizumab can be discontinued [19]. Patients with type I autoimmune CSU experience faster response to omalizumab than type IIb autoimmune CSU. A large real-world US study [26] showed majority of CSU patients started on 300 mg omalizumab dose, were continuously treated for >6 months and without up or down titration for an average of 9 months. 25% of patients that discontinued therapy restarted it. The use of other CU related treatments particularly OCTs was lower after omalizumab commencement [26].

6.9 CSU therapy in special patient groups

The management of CSU in pregnant/lactating women, children and the elderly is largely the same as for non-pregnant adults.

In **pregnant and lactating women** antihistamines should be used at the lowest effective dose [10, 19]. and for the shortest periods of time. SGAs are classified

pregnancy category B by US FDA [10]. All antihistamines are secreted in breast milk and use of FGAs is discouraged during lactation to avoid excessive sedation of the breastfed child [10].

A short course of OCTs may be considered during pregnancy, in case of severe exacerbation. Potential side effects include malformation, neonatal adrenal insufficiency, low birth weight. Although OCTs are secreted in breast milk they are generally considered safe during lactation [10].

Omalizumab is classified pregnancy category B by US FDA [10].

In **children** SGAs rather than FGAs should be used as first line therapy and adjusted for age and weight [10, 19].

OCTs should be avoided where possible and if required only used for 10–14 days because of growth related side effects [10, 19]. The use of omalizumab in adolescents is well supported by the current literature and recommended as step 3 and before the use of ciclosporin in the 2017 urticaria guidelines of EAACI/GA^{2}LEN/EDF/WAO [27].

Ciclosporin is recommended as step 4 and was reported effective in a single open label trial of 7 children aged 9–16 years, at the dose of 3 mg/kg/day in two divided doses for maximum of 8 weeks. Regular monitoring of blood pressure and renal function [10] is required.

There is limited data available regarding the up dosing of SGAs and omalizumab in children with CSU under 12 years of age, and the treatment with cyclosporine and LMAs in paediatric patients of all ages [27].

Therapy of CSU in the **elderly** needs to consider comorbidities, polypharmacotherapy and organ insufficiency and adjusted accordingly [19].

7. Conclusions

In summary CSU is a debilitating disease with a relapsing course. It affects 0.5–1% of the population at any given time. The duration of CSU is generally 1–5 years but can be longer in cases associated with angioedema and autoreactivity. CSU has detrimental effects on quality of life with sleep-deprivation and psychiatric disorders being the most frequent.

In a great number of patients an underlying cause or eliciting factor cannot be identified. Among the patients in which an aetiology is suspected, infections, medication, food and psychological factors are most commonly associated. A potential autoimmune cause has been reported in up to 50% of patients. Urticaria can be presenting sign for many syndromes and associated with several conditions. CINDU is characterised by its ability to be triggered consistently and reproducibly in response to a specific stimulus (pressure, temperature, vibration, water, heat, light).

The diagnosis of CU is often made on clinical grounds, a limited routine diagnostic work-up is recommended in a case-by-case basis.

Antihistamines form the mainstay of therapy. In non-responders a variety of other drugs are available including leukotriene receptor inhibitors, conventional systemic therapy, anti-inflammatory and biologic therapy. Special care must be taken when treating children, pregnant/lactating women and the elderly.

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